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A DOUBLE BLIND CROSS-OVER STUDY OF TWO ORAL FORMULATIONS OF MORPHINE

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1. ABSTRACT

Fifteen patients suffering pain as a result of various malignancie completed this study. Both MST Continus 30mg tablets and morphine sulphat solution (B.P.), were found to be acceptable and on a milligram equivalenc shown to be comparable in their analgesic activity.

Both presentations improved sleep patterns significantly when compare with the duration of sleep recorded prior to the trial. The incidence an severity of side effects for each formulation followed almost identica patterns.

2. INTRODUCTION

There is widespread fear among cancer sufferers and relatives that durin the natural history of the disease pain will become a significant, if no uncontrollable, problem. The incidence and severity of pain tends to b related to the extent, nature and stage of the malignancy. Several studie have shown that the incidence of pain in patients with advanced cancers i approximately 70% (1-4). It is a disquieting fact that many experiencing pai do not have this fully or adequately alleviated (3). It is possible wit existing analgesics and pain treatment options to assure patients that if pai develops it can be removed or at least reduced in intensity.

Extracts from the opium poppy (Papaver somniferum) were used therapeutically by the Sumerians 4,000 years B.C. (5). The chief, active component of the extract, morphine, has been used over the centuries by the ancient Egyptians, Greeks and Romans but it was not until the Seventeenth Century that morphine was introduced to Britain (6).

Morphine has a half-life of 2.2 hours (7) and thus in patients with a persistent cause for their pain the drug must be administered frequently and regularly to prevent the occurrence of break through pain. Formulations containing morphine which have a longer duration of action have been produced

in the past few years. The principle of determining the pharmacokinetics, efficacy and toxicity of any new drug must equally apply to a novel formulation of an existing drug.

Hence this study was designed to determine the efficacy of M.S.T. Continus 30mg tablets in the control of severe pain secondary to cancer and also to assess the incidence and intensity of this preparation's side effects, in comparison with those of standard morphine sulphate solution B.P.

3. PATIENTS, METHODS AND MATERIALS

Eligibility for entry to the study involved the presence of pain of a severity judged to require opiates for control, in patients known to have a histologically documented malignant disease. Twenty-two patients commenced the trial having given their verbal informed consent.

There were nine males and thirteen females, median age fifty-five years. Of these seven were unable to complete the study (two males, five females; median age fifty-seven years). Urea and electrolytes, transaminase and bilirubin levels of all participants were within normal range.

Initially patients were stabilised on M.S.T. Continus 30mg tablets. As this was an outpatient study this procedure took one to two weeks to achieve satisfactory pain control. The patients were then randomised to receive either M.S.T. Continus 30mg tablets and placebo elixir or morphine sulphate solution B.P. in a milligram (mg) equivalent dose plus placebo tablets. After one week of treatment crossover was made to the other regime. Tablets were prescribed twice daily, twelve hours apart, and elixir every four hours. Apart from non-steroidal anti-inflammatory agents all other analgesics were discontinued upon entry. Assessment of pain relief was made by means of a Visual Analogue Scale (V.A.S.) completed by the patient at the following times: stabilisation period, day 0, 3 and 5; first week of study, day 2, 4 and 7; second week, day 9, 11 and 14. In addition duration of sleep was noted prior to stabilisation and throughout the study. Side-effects were scored, again by the patient, on a zero to three scale, three representing the most severe and zero no toxicity. Scoring was performed on a daily basis in a specially designed booklet which also had provision for recording drug compliance. All patients were reviewed weekly throughout the study period.

4. RESULTS

After completion of the trial the mean V.A.S. score after seven da each arm was expressed as a percentage as shown in Table 1.

Table 1. Mean V.A.S. score % after seven days therapy

	Stabilisation	Tablet	Elixir
Sleep	19.07 SD ±14.36	25.00 ±27.45	33.93 ±31.86
Night pain	21.64 ±15.26	25.57 ±29.82	28.79 ±28.99
Day pain	18.93 ±13.77	33.29 ±26.35	33.79 ±28.82

[n = 15. No significant difference exists between scores for stabilisat tablet or elixir. (Students t-test)]

Three patients required fourteen days for stabilisation and thus scor day 14 was used in the calculation.

The effect of the two formulations on hours slept per night is show Table 2.

Table 2.

	Hours of sleep per night
Start of stabilisation	5.21 ± 1.78
After elixir for seven days	6.72 ± 1.54
After tablets for seven days	6.92 ± 2.06

Significance (Student's t-test)

Tablet : Elixir > 0.5
Tablet : Stabilisation <0.05> 0.02
Elixir : Stabilisation <0.05> 0.02

There was no significant difference in the percentage of patients experiencing side effects when on the tablets or the elixir. The most common side effect was transient drowsiness. Constipation was experienced in 71%, with nausea, vomiting and dizziness being the other toxicities encountered.

The intensity of side effects is as shown in Table 3.

Table 3. Intensity of side effects n = 15

		Tablet (mean score)		Elixir (mean score)
A	Drowsiness	10.54	A	9.3
B	Constipation	7.0	B	7.9
C	Nausea	4.7	C	6.5
D	Vomiting	3.5	D	2.9
E	Dizziness	1.5	E	2.0

$P > 0.5$ for A:A ; B:B etc.

Scoring was by means of a zero to three scale with maximum intensity of three for each side effect per 24 hours or twenty one over seven days.

Five patients withdrew from the study (including one who died) during the stabilisation period. One of those five was unable to complete the evaluation form, two had unacceptable nausea and vomiting despite anti-emetics and one patient when randomised refused to continue with the elixir. One patient developed severe pain after randomisation to the active elixir and required hospitalisation for adequate pain control and accordingly was also withdrawn from the study.

5. CONCLUSIONS

To facilitate the cancer patient's endeavour to live his life as near as possible to the standard he "enjoyed" prior to the development of his illness must be one of the paramount aims of those involved in the care of cancer patients. The development of the chronic pain syndrome defeats this objective. Thus the importance of adequate pain relief cannot be overstressed. While it is admitted that no formal attempt was made to assess

the effect of this study on the participant's psychological state and its relationship to the pain experience, it was the impression that those recruited were well adjusted to, and coping reasonably well with, their disease.

No significant difference in V.A.S. score for pain was recorded at the end of seven days stabilisation (on active tablets) after seven days active elixir or after seven days active M.S.T. Continus 30mg tablets. From this we conclude that the formulation of M.S.T. Continus tablets is as efficacious as morphine sulphate solution on a milligram equivalent basis per unit time, providing that the pain process is not altering over the assessment period. Description of pain or its assessment is notoriously difficult, hence the wide S.D. in Table 1. We chose the V.A.S. as one of the most efficient means of quantifying this purely subjective phenomenon (8). The order of incidence of side-effects encountered in this study is much as recorded by Kantor (9). Drowsiness was transient over forty-eight to seventy-two hours and nausea controllable in all but two of the twenty-two patients. Use of a sustained release formulation might reasonably be expected to reduce the intensity and incidence of side effects, if the latter are related to large plasma fluctuations or high peak concentrations of the drug. However, this was not the case and there was no significant difference between the two presentations with respect to side effects.

In conclusion morphine sulphate formulated as M.S.T. Continus 30mg tablets is a generally acceptable preparation which sustains plasma morphine levels (10) and in a mg equivalent dose provides equivalent analgesia to morphine sulphate solution B.P. with a similar intensity and incidence of side effects. The tablet form is more convenient for carriage, and the twice or thrice daily dosage regime may lead to greater patient compliance.

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